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REVIEW ARTICLE

Plants' Natural Products as Alternative Promising Anti-*Candida* Drugs

Sameh Soliman[1,2], Dina Alnajdy[1], Ali A. El-Keblawy[3], Kareem A. Mosa[3,4], Ghalia Khoder[5], Ayman M. Noreddin[6,7]

Departments of [1]Medicinal Chemistry, [5]Pharmaceutics and Pharmaceutical Technology, and [6]Pharmacy Practice and Pharmacotherapy, College of Pharmacy, University of Sharjah, [3]Department of Applied Biology, University of Sharjah, Sharjah, United Arab Emirates, [2]Department of Pharmacognosy, Faculty of Pharmacy, Zagazig University, Zagazig, [4]Department of Biotechnology, Faculty of Agriculture, Al-Azhar University, Cairo, Egypt, [7]Department of Pharmacy Practice, School of Pharmacy, Chapman University, Irvine, California, USA

ABSTRACT

Candida is a serious life-threatening pathogen, particularly with immunocompromised patients. *Candida* infections are considered as a major cause of morbidity and mortality in a broad range of immunocompromised patients. *Candida* infections are common in hospitalized patients and elderly people. The difficulty to eradicate *Candida* infections is owing to its unique switch between yeast and hyphae forms and more likely to biofilm formations that render resistance to antifungal therapy. Plants are known sources of natural medicines. Several plants show significant anti-*Candida* activities and some of them have lower minimum inhibitory concentration, making them promising candidates for anti-*Candida* therapy. However, none of these plant products is marketed for anti-*Candida* therapy because of lack of sufficient information about their efficacy, toxicity, and kinetics. This review revises major plants that have been tested for anti-*Candida* activities with recommendations for further use of some of these plants for more investigation and *in vivo* testing including the use of nanostructure lipid system.

Key words: Anti-*Candida*, biofilm, *Candida*, natural products, plants

INTRODUCTION

Candida is a fungal pathogen[1] which is mostly known to cause high rate of mycotic infection to human worldwide.[2] *Candida* is known to cause mucosal and deep tissue infections. *Candida* infects mucosal tissues including mouth, esophagus, gut, and vagina.[3] Vaginal candidiasis continues to be a world health problem to women.[4] Candidal infections are common in hospitalized patients and elderly people, and are difficult to control.[5] About 50% of adults have *Candida* yeasts in their mouth and it is responsible for superficial easily treated infections. However, candidal infections can spread through the body and become life threatening, in particular with immunocompromised patients.[6,7] Candidiasis represents a major cause of death.[8] *Candida* can switch between two major forms, yeast and hyphae forms. The switch from yeast to hyphae is considered a major infectious agent of *Candida*.[9] In addition, *Candida* spp. produces biofilms on synthetic materials, which facilitates adhesion of the organisms to devices and renders the organism relatively resistant to antifungal therapy.[10] Catheter-associated *Candida* biofilms can lead to bloodstream infections.[11] *Candida*-infected catheters, in particular those associated with microbial biofilms, can represent 90% of infections among hospital-admitted patients and hence considered as a major cause of death.[11] Several synthetic drugs are established in the treatment regimens of candidal infections as indicated in Table 1, however drug resistance is developed.

Correspondence:
Dr. Sameh Soliman,
Department of Medicinal Chemistry, College of Pharmacy,
University of Sharjah, Sharjah, United Arab Emirates.
E-mail: ssoliman@sharjah.ac.ae

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MECHANISMS OF CANDIDAL RESISTANCE TO SYNTHETIC DRUGS

The formation of biofilms in *Candida* and the transition from planktonic to sessile form are mainly associated with highly resistant phenotype. Other mechanisms of resistance include the expression of resistance genes, particularly those encoding efflux pumps, and the presence of persister cells.[17] Major synthetic drugs that develop candidal resistance include 5-flucytosin, amphotericin B, azoles, and echinocandins [Table 1].

PLANTS AS NATURAL SOURCES OF ANTI-CANDIDAL DRUGS

Plants are known for decades as the only source of medicines by traditional people.[18] Moreover, plants are still used as major remedies by several countries, particularly in Africa and Asia.[19] Several plant species showed effective anti-candidal activities [Table 2]. However, promoting a medicinal plant as an antimicrobial agent is challenging and requires more assessment including safety and efficacy prior to clinical study. Table 2 summarizes most of the reported plants tested for anti-candidal activities. Several of these plants showed promising minimum inhibitory concentration (MIC) such as peppermint (0.08 μg/mL),

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Table 1: *Candida* resistance to synthetic drugs

Drug	Mechanism of action	Mechanism of resistance	Reference
5-flucytosine	An antimetabolite that interferes with the fungal thymidylate synthetase	Mutations in the permease enzyme encoded by FCy2 gene which results in impaired uptake of the drug Mutations in the gene FUR1 Alterations in the other enzymes like cytosine deaminase, encoded by the gene FCy1	[12,13]
Amphotericin B	It binds to the fungal ergosterol, and causes pore formation in the cell membrane	A total lack of ergosterol in the fungal membrane or a different ergosterol structure that prevents binding Alterations in the ergosterol biosynthetic pathway (ERG3) lead to the replacement of ergosterol with other sterols with lower affinity for the polyenes	[12,13]
Azoles	Inhibitors of the cytochrome P450 14a-sterol demethylase (CYP51), thus inhibiting biosynthesis of ergosterol	Overexpression of ERG11 and/or mutations in the gene. ERG11 encodes the azole target enzyme, and upregulation can result in resistance due to a nonoptimal enzyme–drug ratio, whereas sequence mutations can cause a decrease in affinity of the enzyme (Erg11p) toward the drug Increased expression of efflux pumps including ABC and MFS Mutations in other ERG genes, in particular ERG3, involved in the biosynthesis of ergosterol	[14,15]
Echinocandins	It is noncompetitive inhibitor of 1,3-β-D-glucan synthase which is responsible for the synthesis of fungal cell wall	Mutations in the FKS genes (FKS1, FKS2, and FKS3) which are related to amino acid substitutions in the 1,3-β-D-glucan synthase (the echinocandins target)	[16]

ATP=Adenosine triphosphate, ABC=ATP-binding cassette, MFS=Major facilitator superfamily

Thymus villosus (0.64 μg/mL), eucalyptus (0.05 μg/mL), lemongrass oil (0.06 μg/mL), *Cinnamomum zeylanicum* (0.01 μg/mL), ginger grass oil (0.08 μg/mL), and coriander (0.2 μg/mL), however they have never been deeply studied as anti-*Candida* drugs for the market use.

This review article provides an overview of the reported natural anti-*Candida* products identified from plants and their mechanisms [Table 2]. Additionally, the current review article explores the possible biotechnological applications for the production of anti-*Candida* drugs and enhancing their activities.

MECHANISM OF ACTION OF ANTI-CANDIDA NATURAL PRODUCTS

The anti-*Candida* mechanisms of action initiated by plant natural products can involve inhibition of germination and biofilm formation, cell metabolism, cell wall integrity, cell membrane plasticity, or can involve induction of apoptosis [Figure 1].

Inhibition of *Candida* biofilm formation and transition to hyphal form

The switch of *Candida* from yeast to hyphae is mainly accompanied by resistant biofilm formation. *Candida* biofilms are difficult to eradicate and are associated with resistance against many existing antifungals. Thymol which is a major constituent of thyme oil can interfere with biofilm metabolic activity and thus inhibits early and mature biofilm formation.[86] Anthraquinones isolated from *Heterophyllaea pustulata* showed significant activity against *Candida tropicalis* biofilm formation by interfering with the pro-oxidant–antioxidant balance leading to biofilm injury.[149] They also showed synergistic activity with amphotericin B. Geranium oil and its nanoemulsion showed antibiofilm activity against *Candida albicans*, *C. tropicalis*, and *Candida glabrata*. The smaller particle size of geranium nanoemulsion efficiently penetrates biofilms and hence damages the organism's cell membrane.[79] Similarly, cinnamic acid derivatives showed great antibiofilm activity against *C. albicans* at lower MIC compared to fluconazole. The most active cinnamic acid derivative is a hybrid of cinnamic acid with miconazole that leads to inhibition of biofilm at 2 μg/mL and reduction in metabolic activity of preformed biofilm at 8 μg/mL.[150,151] Furthermore, lemongrass oil and its major constituents exhibit strong inhibitory activity on *Candida* biofilm formation, germ tube formation (GTF), adherence, and candidal colonization.[130] Many terpenes including carvacrol, geraniol, and thymol showed strong activity in reducing the development of *C. albicans* biofilms. Carvacrol was able to inhibit *Candida* biofilm regardless of the tested species and of the biofilm maturation state.[152]

Inhibition of *Candida* germ tube formation

GTF is a transitional stage between yeast and hyphal cells which is an essential stage for *Candida* virulence activity.[153] GTF increases fungal adherence and penetration to infected tissues.[154] It has been shown that essential oil of oregano inhibits *C. albicans* GTF to a higher extent compared to other essential oils.[33] The inhibition of GTF is mainly related to the lipophilicity of the essential oils and their interaction with the *Candida* cell membrane, leading to changes and loss of the structural and enzymatic constituents of fungal cells including 1,3-β-D-glucan synthases, adenosine triphosphatase (ATPase), mannans, and chitin that are required in GTF.[155,156]

Alteration in *Candida* cell membrane

It has been reported that terpenes can cause alteration in *Candida* cell permeability by getting embedded between the fatty acyl chain in the membrane lipid bilayers and hence interrupting the lipid packing and consequently disturbing membrane structure and functions.[154] Geraniol increases the membrane fluidity by affecting the central part of the lipid bilayers.[157] Tea tree oil increases cell permeability and inhibits medium acidification.[114] *Salvia sclarea* oil and its major constituents, linalyl acetate and linalool, induce a significant increase in plasma membrane fluidity, which in turn induces cell apoptosis. Thymol affects cell membrane electrostatics and can create deviated membrane tension.[84] Coriander oil showed an increase in cell membrane permeability, loss of membrane potential, leakage of intracellular DNA, and damage of cytoplasmic membrane, thus causing impaired cellular functions.[84] *Raphanus sativus* antifungal peptide 2 (RsAFP2) is a plant defensin that can interact with the sphingolipid glucosylceramide (GlcCer) of susceptible fungal membranes but not with the human GlcCer, and hence can exhibit

Table 2: Natural anti-*Candida* products, their botanical sources, and minimum inhibitory concentration

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
Anacardiaceae	Marula	*S. birrea*	South Africa and Madagascar	Oleic acid	*C. parapsilosis*	210	[20]
	Sicilian sumac	*R. coriaria*	Southern parts of Europe	Phenols	*C. albicans*	15,000	[21]
Annonaceae	Bushveld bitterwood	*X. parviflora*	Sudan, Uganda, southern region of Kenya, Malawi, Mozambique, Zimbabwe, and Limpopo	β-pinene	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis* *C. lusitaniae*	6250 3120 1560	[22]
	False nutmeg or calabash nutmeg	*M. myristica*	Evergreen forests of Liberia to Nigeria and Cameroon, Ghana, Angola, and Uganda	Linear aliphatic primary alcohols, n-hexacosanol, diunsaturated linear 1,2-diols α-phellandrene and α-pinene	*C. albicans* *C. krusei*	1.6	[22]
	Sugar apple or custard apple	*A. squamosa*	Native to the tropical Americas and West Indies	Diterpenoid compound kaur-16-en-18-oic acid, α-pinene, sabinene, and limonene	*C. albicans*	Methanol and chloroform extracts: 600 and aqueous extract: 800	[23,24]
	Ethiopian pepper	*X. aethiopica*	Senegal, Sudan, Angola, Congo, Zambia, and Mozambique	β-pinene and β-phellandrene + 1,8-cineole	*C. albicans* *C. krusei* *C. parapsilosis* *C. tropicalis*	3120	[22]
Anisophylleaceae	Monkey apple	*A. laurina*	Africa, India, Sri Lanka, mainland Southeast Asia, Sumatra and Borneo	Seeds and pulps are rich in flavonoids, phenolics, citric acid, malic acid, tartaric acid, fumaric acids, oxalates, phytic acid, and tannins. The seeds and pulp oils were also found to be rich in unsaturated fatty acids	*C. albicans*	Methanol extract: 500 Ethanol extract: 1000	[25,26]
Acanthaceae	Firecracker flower	*C. infundibuliformis*	India and Sri Lanka	Ethyl acetate	*C. krusei*	125,000	[27]
	False waterwillow	*A. paniculataa*	Native to India and Sri Lanka	14-deoxy-11,12-didehydroandrographolide	*C. krusei* *C. albicans* *C. tropicalis*	250 100	[28]
Acoraceae	Sweet flag or calamus	*A. calamus*	North temperate hemisphere and Tropical Asia	Triploid and tetraploid	*C. albicans* *C. krusei* *C. lusitaniae* *C. parapsilosis*	12,500	[29]
				Flavonoids and lectins	*C. albicans*	28,800	[30]
Amaryllidaceae	Garlic	*A. sativum*	Native to Asia	Allicin	*C. albicans*	200-500	[31,32]
	Onion	*A. cepa*	Native to China	Tannins and flavonoids like quercetin		10,000	[31,32]
Apiaceae	Coriander	*C. sativum*	Native to the Mediterranean region	Linalool, 1-decanol, 2E-decenol, 2 Z-dodecenol, aldehydes, 3-hexenol	*C. albicans ATCC 90028*	0.2	[33,34]
	Cumin	*C. cyminum*	Native to Asia	Pinene, cineole, linalool	*C. albicans*	280	[35]
	Fennel	*F. vulgare*	Native to the Mmediterranean region	Trans-anethole, limonene, fenchone	*C. albicans*	300	[36]
	Persian hogweed	*H. persicum*	Native to Iran	Anethole, terpinolene	*C. albicans*	1100	[37]
	Anise	*P. anisum*	Native to the Mmediterranean region	Anethole, coumarins	*C. albicans*	300	[38]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
Apocynaceae	White's ginger	*M. whitei*	Tropical Africa	Alkaloids, anthocyanins	*C. guilliermondii*	6250	[39]
				Anthraquinones, flavonoids	*C. albicans*	3120	
				Phenols, saponins	*C. lusitaniae*		
					C. tropicalis		
	Silk rubber	*Funtumia elastica*	Senegal and Tanzania	Tannins and flavonoids	*C. albicans*	100,000	[40]
Arecaceae	Coconut	*C. nucifera*	Native to Pacific Islands (Melanesia). But cultivated through the tropics	Lauric acid, caprylic acid, and capric acid	*C. glabrata*	25% (1:4 dilution)	[41]
					C. tropicalis		
					C. parapsilosis		
					C. stellatoidea		
					C. krusei		
					C. albicans		
	Dhangri bet or Rab bet	*C. leptospadix*	Himalayas, Nepal, and Bengal	Ursolic acid (triterpenoid saponin)	*C. albicans*	60	[42]
Asteraceae	Wormwood	*A. sieberi*	Central and Southw West Asia	β-thujone, camphor,e α-thujone	*C. glabrata*	37.4-4781.3	[43]
	Wild rhubarb or lesser burdock	*A. minus*	Native to Europe, but has become an invasive weed in Australia, North and South America	Major flavonoids (isoquercitrin and rutin), and five minor flavonoids (astragalin, kaempferol 3-O-rhamnoglucoside, quercetin 7-O-glucoside, an isomer of quercitrin, and quercetin 3-O-arabinoside), and arctiin	*C. albicans*	12,500	[44,45]
					C. dubliniensis		
					C. glabrata		
					C. krusei	12,500	
					C. stellatoidea		
					C. tropicalis	25,000	
	Field wormwood	*A. campestris*	North America	Luteolin-7-O-rutinoside in MCE	*C. glabrata*	25,000	[29]
					C. lusitaniae		
					C. tropicalis	50,000	
					C. krusei		
					C. parapsilosis		
	Fringed sagebrush or pasture sage	*A. frigida*	Native to Europe, Asia, and much of North America	5-ethenyltetrahydro-5-methyl-2-furanyl moiety	*C. parapsilosis*	50,000	[29]
					C. lusitaniae	12,500	
					C. krusei	6000	
					C. tropicalis		
					C. glabrata	400	
	Tall goldenrod or Giant goldenrod	*S. gigantea*	North America	Oleanolic acid and kaempferol	*C. tropicalis*	12,500	[29]
					C. lusitaniae		
					C. albicans	1600	
					C. krusei	800	
					C. glabrata	100	
	Yarrow	*A. biebersteinii*	Native to Europe, Asia, and North America	Limonene	*C. albicans*	100,000	[46]
Betulaceae	Green alder	*A. viridis*	Distributed widely across the cooler parts of the Northern Hemisphere	Mineral acids	*C. albicans*	12,500	[29]
					C. glabrata	25,000	
					C. parapsilosis		
					C. krusei	200	
					C. lusitaniae	6000	
	Yellow birch	*B. alleghaniensis*	North America	Triterpene squalene and aliphatic hydrocarbon tetracosan	*C. parapsilosis*	3000	[29]
					C. albicans	800	
					C. krusei	400	
					C. lusitaniae		
					C. glabrata	50	

Contd...

Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
Bignoniaceae	Golden bell-bean	*M. obtusifolia*	From Angola and Namibia eastwards and from the DRC and Kenya southwards to South Africa, including Malawi, Mozambique, and Zambia	Ursolic acid, pomolic acid and 2-epi-tormentic acid	*C. albicans*	Pomolic acid: 12.5-25 Plant extract: 160-320 Ursolic acid: 50-100 2-epi-tormentic acid: 50-100	[47]
	Flame vine	*P. venusta*	Native to Brazil and Paraguay	Isoverbascoside, verbascoside, quercetin-3-O-x-L rhamnopyranosyl-(1-6)-b-D-galactopyranoside	*C. krusei ATCC 6258* *C. krusei USP 2223* *C. albicans ATCC 10231* *C. albicans USP* *C. albicans of C. parapsilosis USP 1933* *C. tropicalis USP* *C. guilliermondii USP 2234*	Crude extract: 3-24 Isoverbasco-side: 0.7-6 Verbasco-side: 0.7-1.5 Quercetin: 6	[48]
	Cricket vine	*A. chica*	Cerrado, Atlantic Forest, and the Amazon Region	Phenolics, flavonoids, anthocyanins, β-carotenes, and lycopenes	*C. glabrata* *C. rugosa* *C. albicans*	Dichloromethane extract: 7-30 500	[49]
	Pink trumpet tree or lavender trumpet tree	*T. avellanedae*	America, Mexico, and Argentina	Naphthoquinones	*C. albicans*	Methanol extract: 1-15	[50]
Caesalpiniaceae	Divida	*S. zenkeri*	Africa and Madagascar-Gabon	2,4,5,7-tetrathiaoctane	*C. guilliermondii* *C. parapsilosis* *C. tropicalis* *C. glabrata* *C. krusei* *C. lusitaniae* *C. albicans*	6250 4680 3900 2340	[51]
Caricaceae	Papaya	*C. papaya*	Tropical America	Enzymes like α-D-mannosidase and glucosaminidase	*C. albicans*	250	[52,53]
Combretaceae	Tanibuca	*B. tomentosa*	South America Brazil, Bolivia, and Peru	Gallic acid	*C. albicans* *C. tropicalis* *C. krusei* *C. glabrata* *C. parapsilosis* *C. dubliniensis*	200-12,500	[54]
	Bushwillow	*C. albopunctatum*	Southern Africa	Terpenoids, flavonoids, phenanthrenes, and stilbenoids	*C. albicans*	640	[55-58]
		C. imberbe	Tropical Africa southward to Namibia and Botswana	Pentacyclic tritepenes, hydroxyimberbic acid		2500	
		C. nelsonii		Asiatic acid and arjunolic acid		40	
	Myrobalan or beach almond	*T. bellirica*	Indian subcontinent and Thailand	Termilignan, thannilignan, 7-hydroxy-3,4-(methylenedioxy) flavan, anolignan B	*C. albicans*	1-3	[59]

Contd...

Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
Curtisiaceae	Assegai tree	*C. dentata*	Zimbabwe, Mozambique, South Africa, and Swaziland	Phenols, flavonoids, tannic acid, saponins, steroids, and alkaloids	*C. albicans*	Leaf extract: 111 Stem bark extract: 610	[60,61]
Cucurbitaceae	Bitter apple or bitter cucumber	*C. colocynthis*	Tropical and sSubtropical North Africa and Asia	Glucosides and resins	*C. albicans* *C. glabrata* *C. krusei* *C. parapsilosis* *C. guilliermondii* *C. tropicalis* *C. dubliniensis*	3125-12,500	[16]
Ebenaceae	Gabon ebony	*D. crassiflora*	Endemic to Western Africa	Isoarborinol methyl ether (cylindrin)	*C. glabrata* *C. albicans* *C. krusei* *C. tropicalis*	25,000 12,500	[62]
	Evergreen tree	*D. canaliculata*		Plumbagin and two known pentacyclic triterpenes (lupeol and lupenone)	*C. albicans* *C. kefyr* *C. parapsilosis*	Plant extract 12.5 25 12.5 Plumbagin 0.78-3.12	[63]
Ephedraceae	Joint-pine or Bbrigham tea	*E. pachyclada* *E. procera* *E. strobilacea*	Native to southwestern North America, southern region of Europe, and northern regions of Africa	- - -	*C. albicans* *C. albicans* *C. albicans*	0.5 0.5 1	[64]
Eriocaulaceae	Leiothrix	*L. spiralis*	South America	8-carboxy-methyl-1,3,5,6-tetrahydroxyxanthone	*C. albicans* *C. krusei* *C. parapsilosis* *C. tropicalis*	62.5 15.7 15.7 31.25	[65]
Euphorbiaceae	Pillpod sandmat	*E. hirta*	Native to India	β-amyrin, and 24-methylenecycloartenol	*C. albicans*	3130	[66]
	Red sacaca	*C. cajucara*	Brazil	Linalool	*C. albicans (ATCC 51501)*	13.4	[67]
	Prostrate spurge or blue weed	*E. prostrata*	Native to the Caribbean and certain parts of South America	Flavonoids likesuch as apigenin-7-glycoside, luteolin-7-glycoside, and quercetin Pphenolic compounds such aslike ellagic acid, gallic acid, and tannins	*C. albicans*	Hydroalcoholic extract: 63 Ethyl acetate extract: 16	[66,68]
Fabaceae	Prekese	*T. tetraptera*	Native to Western Africa	Oleanolic glycosides and cinnamic acids	*C. glabrata* *C. krusei* *C. tropicalis* *C. albicans* *C. guilliermondii* *C. lusitaniae* *C. parapsilosis*	6250 3120	[69]
	Red propolis	*D. ecastaphyllum*	Native to the tropical regions of Central and South America and Africa	Formononetin	*C. albicans ATCC 76645* *C. albicans* LMP-20 *C. tropicalis*	25	[70]

Contd...

Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (µg/mL)	Reference
	Albizia	*A. myriophylla*	Asia, Africa, Madagascar, America, and Australia	Flavan-3,4-diol, lupinifolin, dihydroxy derivatives, and lignan glycosides	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis*	100–400	[71]
	Naranjito	*S. simplex*	Savannas	Diterpenes	*C. albicans*	32	[72]
	Golden shower tree	*C. fistula*	Native to the Indian subcontinent	Cassic acid (rhein) and other phenolic compounds	*C. albicans* *C. glabrata* *C. tropicalis*	Seed extract: 300–350 Fruit extract: 100–250	[73,74]
	Licorice	*G. glabra*	Native to southern region of Europe and India	Formononetin, liquiritigenin, and apigenin	*C. albicans* *C. glabrata* *C. parapsilosis* *C. tropicali*	187.5 1500	[75]
	Senna	*C. alata*	Native to South America	Chrysoeriol and stearic acid	*C. albicans*	26900	[76]
	Salt-tree	*H. halodendron*	Native to Russia and Ssouthern Asia	Salicylic acid, p-hydroxybenzoic acid (ferulic acid) and 4-hydroxy-3-methoxy cinnamic acid	*C. albicans*	Salicylic acid: 150 Benzoic acid: 100 4-hydroxy-3-methoxy cinnamic acid: 20	[77]
Gentianaceae	Common centaury	*C. erythraea*	Europe and Africa	Ferulic and sinapic acids	*C. albicans*	100	[78]
	Lesser centaury	*C. pulchellum*	Europe and Mediterranean region	Xanthone demethyleustomin	*C. albicans*	400	
	Spiked centaury	*C. spicatum*	Mediterranean region and Europe	Sweroside	*C. albicans*	200	
	Slender centaury	*C. tenuiflorum*	Europe and Asia	Secoiridoid glycosides	*C. albicans*	200	
Geraniaceae	Rose geranium	*P. graveolens*	Zimbabwe and South Africa	Geraniol and linalool	*C. tropicalis*	125	[79]
Grossulariaceae	European gooseberry	*R. uva-crispa*	Europe and Africa	Citric acid	*C. lipolytica* *C. glabrata*	4630 4600	[80]
	Black currant	*R. nigrum*	Native to temperate parts of central and northern regions of Europe	Gamma-linolenic acid and alpha-linolenic acid	*C. tropicalis* *C. guilliermondii* *C. inconspicua* *C. parapsilosis*	7160 6130 4220 4410	[80]
Juglandaceae	Persian walnut	*J. regia*	Central Asia	Juglone	*C. albicans*	6	[81]
Lamiaceae	Texas sage	*S. texana*	Native to the US states of Texas and New Mexico and in northern part of Mexico	Polyphenolic flavonoids and phenolic acids. Flavones, flavonols, and their glycosides constitute the majority of flavonoids. Malonylated anthocyanins are abundant in red -to -blue salvia flowers	*C. albicans*	Hydroalcoholic extract: 125 Ethyl acetate extract: 62	[82,83]
	Peppermint	*M. piperita*	Europe and Middle East	Menthol, menthyl acetate, and menthofuran	*C. albicans ATCC 10231*	0.08	[21]
	Thyme	*T. maroccanus* *T. broussonetii*	Native to temperate regions in Europe, North Africa, and Asia	Thymol, carvacrol	*C. albicans ATCC 3153A* *C. albicans ATCC MYA2876*	125	[84,85]
		T. villosus		Geranyl acetate, terpinen-4-ol, linalool, and geraniol	*C. albicans ATCC 10231*	0.64	[86]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (µg/mL)	Reference
	Oregano	*O. vulgare*	Eurasia and Mediterranean region	Carvacrol, β-fenchyl alcohol, thymol, and γ-terpinene	*C. albicans*	50-100	[43,87,88]
	Mediterranean thyme	*T. capitata*	Mediterranean region	Carvacrol	*C. albicans* *C. glabrata* *C. tropicalis*	0.32	[89]
	Holy basil	*O. sanctum*	Native to Indian subcontinent and cultivated throughout tropical Asia	Methyl chavicol and linalool	*C. albicans* *C. tropicalis* *C. glabrata* *C. parapsilosis* *C. krusei*	0.015%-0.045%v/v	[90]
	Rosemary	*R. officinalis*	Native to the Mediterranean region	P-cymene, linalool, gamma-terpinene, thymol, beta-pinene, alpha-pinene, and eucalyptol	*C. albicans* *C. dubliniensis* *C. parapsilosis* *C. tropicalis* *C. guilliermondii* *C. utilis* *C. krusei* *C. lusitaniae* *C. glabrata* *C. rugosa*	Methanol extract: 1-7 Dichloro-methane extract: 7-30	[91,92]
	Ginger bush	*T. riparia*	Native of South Africa	14-hydroxy-9-epi-caryophyllene, calyculone, cis-muurolol-5-en-4-α-ol, fenchone, and α-trans-bergamotene	*C. tropicalis*	250	[93]
	Hyssop	*H. officinalis*	Native to sSouthern region of Europe, the Middle East, and the region surrounding the Caspian Sea	B-pinene, 1,8-cineole, isopinocamphone	*C. albicans*	Aqueous and ethyl acetate extract: 7000 Methanolic extract: 10,000	[94]
	Patchouli	*P. cablin*	Native to tropical regions of Asia	Pogostone	*C. albicans* *C. parapsilosis* *C. famata* *C. guilliermondii*	3.13-50 50 12.5 100	[95]
	Basil	*O. basilicum*	Native to Mediterranean rRegion and India	Linalool, 1,8-cineole , camphor, eugenol, (Z)-caryophyllene, limonene, b-pinene, camphene, α-pinene	*C. albicans* *C. dubliniensis*	800-1600 400-1600	[90]
	Sage	*S. officinalis*	Native to the Mediterranean region	Cis-tujhonethujone , trans- thujonetujhone, camphor, borneol, 1,8-cineole, a-pinene, camphene, b-pinene	*C. albicans* *C. dubliniensis*	800-3200 800-3200	[82]
				Cineole and borneol	*C. parapsilosis* *C. tropicalis*	2500 1250	[96]
				7-methoxyrosmanol and galdosol	*C. clus* *C. tropicalis*	160	[83]
	Avishan	*Z. multiflora*	Iran and Afghanistan	Thymol, carvacrol	*C. albicans*	150	[85]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
	Baikal Skullcap	*S. baicalensis*	Native to North America	Scutellarin	*C. albicans*	5000 200	[97]
	Ornamental oregano	*M. laevigatum*	Caribbean Sea and Mexico	-	*C. albicans*	100	[98]
	Spiked thyme	*T. spicata*	Native to the Mediterranean region of Europe, North Africa, and the Middle East	Carvacrol	*C. albicans* *C. clus* *C. glabrata* *C. krusei* *C. parapsilosis* *C. tropicalis*	40 10	[96]
Lindsaeaceae	Stenoloma	*S. chusanum*	China	Syringic acid, vanillic acid, and gentisic acid	*C. albicans*	50	[99]
Lauraceae	Cinnamon	*C. zeylanicum*	South- West India and Sri Lanka	Cinnamaldehyde, benzaldehyde, cinnamyl acetate	*C. albicans ATCC 10231* *C. albicans ATCC 90028* *C. albicans* *C. glabrata* *C. parapsilosis* *C. guilliermondii* *C. krusei* *C. lusitaniae* *C. tropicalis*	0.01 10.45 1120 3120 780 97	[100,101]
	Bay laurel or Laurel	*L. nobilis*	Native to the Mediterranean region	1,8-cineole	*C. holmii* *C. albicans* *C. glabrata* *C. insane* *C. krusei* *C. tropicalis*	160 130 700 40	[96]
Lythraceae	Pomegranate	*P. granatum*	Native to Iran and northeast regions of Turkey	Anthocyanins, and hydrolysable tannins Triacylglycerols Punicalagin	*C. lusitaniae* *C. glabrata* *C. rugosa* *C. albicans* *C. parapsilosis*	1 125 250 3.9 1.9	[102,103]
	Mangrove apple	*S. alba*	Seychelles and Madagascar	Lupeol and oleanic acid	*C. albicans*	250	[104]
Malvaceae	Sorrel or roselle	*H. sabdariffa*	Native to Tropical Africa	Flavonoids and cyaniding proanthocyanidin	*C. albicans*	0.5-2	[105]
Menispermaceae	Han Fang Ji	*S. tetrandra*	China	Tetrandrine	*C. albicans*	0.125-16	[106]
Moraceae	Dorstenia	*D. turbinata*	Upper and lLower Guinea	(2'S, 3'R)-3'-hydroxymarmesin	*C. albicans* *C. glabrata*	39	[107]
	Bubu Fig	*F. bubu Warb*	Coastal Tanzania	Trans-resveratrol 4a and piceid 7a	*C. albicans*	9.8	[52,108]
	Brown-woolly fig	*F. drupacea*	Mediterranean region	5-O-methyllatifolin, epifriedelanol, friedelin	*C. albicans*	Hexane extract: 13	[109]
	Banjo fig or fiddle-leaf fig	*F. lyrata*	Native to tropical Africa	Alkaloids, flavonoids, coumarins, saponins, and terpenes	*C. albicans*	50-2500	[110]
	Common dorstenia	*D. psilurus*	Angola, Cameroon, Uganda, Tanzania, Malawi, and Mozambique	Dorsilurin F	*C. glabrata* *C. krusei* *C. lusitaniae* *C. guilliermondii* *C. albicans* *C. tropicalis*	3120 1560 390	[107]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (µg/mL)	Reference
Myrtaceae	Gum coolibah	*E. intertexta*	Native to Australia	1,8-cineole	*C. albicans*	62.5	[111]
	Eucalyptus	*E. globulus*	Native to Australia	1,8-cineole, limonene, p-cymene γ-terpinene, α-pinene, and α-phellandrene	*C. albicans*	0.05	[112]
	Clove	*S. aromaticum*	Native to Indonesia	Eugenol, thymol	*C. albicans ATCC 10231*	500	[113]
	Australian tea tree	*M. alternifolia*	Native to Australia	Terpinen-4-ol γ-terpinene α-terpinene 1,8-cineole	*C. albicans*	20.03 2.25-112.5	[114,115] [116]
	Jambolan tree	*S. cumini*	Native to Bangladesh, India, Nepal, Pakistan, Sri Lanka, Malaysia, the Philippines, and Indonesia	Gallic, ellagic acid polyphenol derivatives, acylated flavonol glycosides, kaempferol, myricetin, and other polyphenols	*C. albicans* *C. dubliniensis* *C. parapsilosis* *C. tropicalis* *C. guilliermondii* *C. utilis* *C. krusei* *C. lusitaniae* *C. glabrata* *C. rugosa*	Methanol extract: 1	[113,117]
	Red ironbark	*E. sideroxylon*	Native to Australia	Leucocyanidin and 1,8-cineole	*C. albicans*	400,000	[118]
	Coral Gum	*E. torquata*	Australia	1,8-cineole	*C. albicans*	400,000	[118]
	Flooded Gum	*E. largiflorens*	Native to Australia	1,8-cineole	*C. albicans*	31.2	[111]
Nitrariaceae	Syrian rue or Wild Rue	*P. harmala*	Asian origin and grows in the Middle East and in part of South Asia mainly in India and Pakistan	Alkaloids such as harmalin, harmalol, harmine, and harmane	*C. albicans* *C. parapsilosis* *C. keiffir* *C. glabrata* *C. tropicalis* *C. dubliniensis*	Plant extract: 312-1250 Harmane: 583 Harmine: 500 Harmaline: 600 Harmalol: 750	[119,120]
Olacaceae	Upper Vvolta	*O. subscorpioidea*	Mostly in forests, but extending far into the Ssavannah regions	-	*C. glabrata* *C. krusei* *C. guilliermondii* *C. parapsilosis* *C. lusitaniae* *C. albicans* *C. tropicalis*	1560 780 390 190 97 48	[121]
Onagraceae	Willow herb	*E. angustifolium*	Native to the temperate Northern Hemisphere and forests	Oenothein B	*C. albicans* *C. krusei* *C. parapsilosis* *C. lusitaniae* *C. glabrata*	200-400 100 400 50 25	[29]
Paeoniaceae	Rock's peony	*P. rockii*	Gansu and China	Taxifolin Gallic acid	*C. albicans* *C. albicans*	25 30	[122]
Plantaginaceae	Ribwort Plantain	*P. lanceolata*	Native to Eurasia and South America	Acteoside (verbascoside) and cistanoside F	*C. albicans*	200,000	[123]
Plumbaginaceae	Doctorbush or wild leadwort	*P. scandens*		Plumbagin (naphthoquinon)	*C. albicans*	0.78	[124]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (µg/mL)	Reference
Piperaceae	Pepper	*P. bredemeyeri*	Native to Columbia and Venezuela	Trans-β-caryophyllene, caryophyllene oxide, β-pinene and α-pinene	*C. albicans* *(Clinical isolate)*	157.5-222.7	[125,126]
	Wild pepper	*P. capense*	Guinea east to Ethiopia and south to Angola	Monoterpene hydrocarbons	*C. albicans*	3120	[126]
					C. guilliermondii		
					C. krusei		
					C. parapsilosis		
					C. lusitaniae	1560	
	Black pepper	*P. nigrum*	India	BHA	*C. albicans*	12,500	[126]
	Lacquered pepper	*P. regnellii*	Brazil	Ethyl acetate	*C. krusei*	500	[126,127]
					C. albicans	125	
	West African pepper	*P. guineense*	West Africa	Beta-caryophyllene	*C. parapsilosis*	6250	[126,128]
					C. albicans	3120	
					C. glabrata		
					C. tropicalis		
					C. lusitaniae	1560	
Poaceae	Ginger grass oil	*C. martinii*	India and Pakistan	Geraniol, (E)-β-ocimene and geranyl acetate	*C. albicans*	0.15	[129]
	Lemongrass oil	*C. citratus*	Southeast Asia	Geranial, neral, and myrcene	*C. albicans* *ATCC 10231*	0.06	[130,131]
	Cogongrass	*I. cylindrica*	Native to Ssouth America,ern North America, and Central America, and South America	Arundoin and 1-(3,4,5-trimethoxyphenyl)-1,2,3-propanetriol	*C. albicans*	6250	[132]
					C. parapsilosis		
					C. glabrata	3120	
					C. guilliermondii		
					C. lusitaniae		
					C. tropicalis		
					C. krusei	1560	
Pteridaceae	Venus hairfern	*A. capillus-veneris*	Native to southern half of the US through Mexico	Flavonoids, sulfphate esters of hydroxycinnamic acid-sugars, different classes of triterpenoids, sterols, quinic and shikimic acids	*C. albicans*	1000	[133,134]
Ranunculaceae	Common fennel flower	*N. sativa*	Native to Asia	P-cymene, thymol	*C. albicans*	2300	[135]
Rhamnaceae	Sierra nakedwood	*C. greggii*	Native to the lower Rio Grande Valley of Texas and Mexico	Chrysophanol	*C. albicans*	Hydroalcoholic extract: 125 Ethyl acetate extract: 62	[136]
Rosaceae	Virginia strawberry	*F. virginiana*	North America, in the United States (including Alaska) and Canada	Hydroxybenzoic acid and flavonols	*C. albicans*	800	[29]
					C. tropicalis		
					C. parapsilosis	200	
					C. lusitaniae	100	
					C. glabrata	50	
					C. krusei		
Rubiaceae	Great morinda	*M. citrifolia*	Asia and Australia	6α-hydroxyadoxoside and americanin A	*C. albicans*	40,000	[137]
	Morinda	*M. morindoides*	All tropical regions of the world	Kaempferol 3- rhamnoside and chrysoeriol 7-neohesperidoside	*C. albicans*	62,500	[138]
Salicaceae	Quaking aspen	*P. tremuloides*	North America	Salicortin	*C. albicans*	1600	[29]
					C. tropicalis		
					C. parapsilosis	400	
					C. krusei	200	
					C. lusitaniae		
					C. glabrata	25	

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (µg/mL)	Reference
Salvadoraceae	Toothbrush tree	*S. persica*	Native to Middle East	Camphor and cineole	*C. albicans* *C. dubliniensis*	4900 20,000	[35]
Sapindaceae	Western soapberry	*S. saponaria*	Native to the Americas	Carbohydrates and triterpenes	*C. parapsilosis*	160	[139]
	Guarana	*P. cupana*	Amazon and Brazil	(+)-catechin and (-)-epicatechin	*C. albicans*	500	[140]
Sargassaceae	Brown algae	*S. wightii*	Distributed throughout the temperate and tropical oceans of the world	Sulfphur	*C. albicans* *C. glabrata* *C. guilliermondii* *C. krusei* *C. parapsilosis* *C. tropicalis*	100,000	[113]
Simaroubaceae	Brucea fruit or Java Brucea	*B. javanica*	Naturally from Sri Lanka and India to China, Malesia, New Guinea, and Australia	Triterpenoid	*C. albicans* *C. krusei* *C. tropicalis* *C. glabrata* *C. lusitaniae* *C. parapsilosis* *C. dubliniensis*	50,000 25,000 3130	[141]
Solanaceae	Black nightshade	*S. nigrum*	Native to Tropical Africa	Glycoprotein (glycine and proline)	*C. glrabrata* *C. albicans* *C. tropicalis*	1000 200	[31]
	Eggplant	*S. melongena*	Savannahs, Asia, and Africa	4α-methylsterols and vanillin	*C. guilliermondii* *C. tropicalis*	6250 3120	[142]
	Chinese boxthorn or wolfberry	*L. chinense*	Native to China	Dihydro-N-caffeoyltyramine, cis-N caffeoyltyramineb, trans-N-feruloyloctopamine, trans-N-caffeoyltyramineb	*C. albicans*	5 40 10 5	[143]
Theaceae	White tea	*C. sinensis*	East and South Asia	Catechins and caffeine	*C. albicans*	10,000	[144]
Verbenaceae	Mexican oregano	*L. graveolens*	The United States and Mexico	Carvacrol, thymol, and p-cymene	*C. albicans*	100-200	[145]
	Brazilian Oregano	*L. origanoides*	Brazil	Oxygenated monoterpenes, carvacrol, and thymol	*C. albicans*	157.5-198.4	[146]
Xanthorrhoeaceae	*A. vera*	*A. barbadensis*	Mediterranean region of Europe and Africa	Amino acids and acemannan	*C. albicans* *C. glabrata* *C. tropicalis*	1000 200	[31]
Zingiberaceae	Turmeric	*C. longa*	Native to Ssouthwest India	Curcumin	*Candida*	250-2000	[147]
	Ginger	*Z. officinale*	Native origin unknown, but widely cultivated in the tropics and subtropics	α-curcumene, zingiberene, α-farnesene, β-bisabolene sesquiphellandrene, neral, and geranial	*C. albicans* *C. dubliniensis*	400-1600 400-800	[148]
	Alligator pepper	*A. citratum*	Widespread across tropical Africa as well as on some islands of the Indian Ocean	Oxygenated components belonging to the acyclic terpene class, such as geraniol	*C. tropicalis* *C. parapsilosis* *C. glabrata* *C. guilliermondii* *C. albicans* *C. lusitaniae* *C. krusei*	6250 4680 3120 780 390	[38]

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Table 2: Contd...

Plant family	Plant common name	Botanical name	Natural habitat	Main active constituents	*Candida* species	MIC (μg/mL)	Reference
	Melegueta pepper	*A. melegueta*		α- and β-caryophyllene	*C. albicans*	6250	[38]
					C. krusei		
					C. parapsilosis	3120	
					C. lusitaniae	1560	
					C. tropicalis		
					C. guilliermondii		

MIC=Minimum inhibitory concentration, *C. infundibuliformis*=*Crossandra infundibuliformis*, *A. paniculataa*=*Andrographis paniculataa*, *A. calamus*=*Acorus calamus*, *A. sativum*=*Allium sativum*, *A. cepa*=*Allium cepa*, *C. sativum*=*Coriandrum sativum*, *C. cyminum*=*Cuminum cyminum*, *F. vulgare*=*Foeniculum vulgare*, *H. persicum*=*Heracleum persicum*, *P. anisum*=*Pimpinella anisum*, *M. whitei*=*Mondia whitei*, *F. elastic*=*Funtumia elastic*, *C. nucifera*=*Cocos nucifera*, *C. leptospadix*=*Calamus leptospadix*, *A. sieberi*=*Artemisia sieberi*, *A. minus*=*Arctium minus*, *A. campestris*=*Artemisia campestris*, *A. frigida*=*Artemisia frigida*, *S. gigantean*=*Solidago gigantean*, *A. biebersteinii*=*Achillea biebersteinii*, MCE=Methanolic crude extract, *A. viridis*=*Alnus viridis*, *B. alleghaniensis*=*Betula alleghaniensis*, *M. obtusifolia*=*Markhamia obtusifolia*, DRC=Democratic Republic of the Congo, *P. venusta*=*Pyrostegia venusta*, *A. chica*=*Arrabidaea chica*, *T. avellanedae*=*Tabebuia avellanedae*, *S. zenkeri*=*Scorodophloeus zenkeri*, *C. papaya*=*Carica papaya*, *B. tomentosa*=*Buchenavia tomentosa*, *C. albopunctatum*=*Combretum albopunctatum*, *C. imberbe*=*Combretum imberbe*, *C. nelsonii*=*Combretum nelsonii*, *T. bellirica*=*Terminalia bellirica*, *C. dentate*=*Curtisia dentate*, *C. colocynthis*=*Citrullus colocynthis*, *D. crassiflora*=*Diospyros crassiflora*, *D. canaliculata*=*Diospyros canaliculata*, *E. pachyclada*=*Ephedra pachyclada*, *E. procera*=*Ephedra procera*, *E. strobilacea*=*Ephedra strobilacea*, *L. spiralis*=*Leiothrix spiralis*, *E. hirta*=*Euphorbia hirta*, *C. cajucara*=*Croton cajucara*, *E. prostrate*=*Euphorbia prostrate*, *T. tetraptera*=*Tetrapleura tetraptera*, *D. ecastaphyllum*=*Dalbergia ecastaphyllum*, *A. myriophylla*=*Albizia myriophylla*, *S. simplex*=*Swartzia simplex*, *C. fistula*=*Cassia fistula*, *G. glabra*=*Glycyrrhiza glabra*, *C. alata*=*Cassia alata*, *H. halodendron*=*Halimodendron halodendron*, LMP=Lysosomal membrane permeabilization, *C. erythraea*=*Centaurium erythraea*, *C. pulchellum*=*Centaurium pulchellum*, *C. spicatum*=*Centaurium spicatum*, *C. tenuiflorum*=*Centaurium tenuiflorum*, *P. graveolens*=*Pelargonium graveolens*, *R. uva-crispa*=*Ribes uva-crispa*, *R. nigrum*=*Ribes nigrum*, *S. texana*=*Salvia texana*, *M. piperita*=*Mentha piperita*, *T. maroccanus*=*Thymus maroccanus*, *T. broussonetii*=*Thymus broussonetii*, *T. villosus*=*Thymus villosus*, *O. Vulgare*=*Origanum Vulgare*, *T. capitata*=*Thymbra capitata*, *J. regia*=*Juglans regia*, *O. sanctum*=*Ocimum sanctum*, *R. officinalis*=*Rosmarinus officinalis*, *T. riparia*=*Tetradenia riparia*, *H. officinalis*=*Hyssopus officinalis*, *P. cablin*=*Pogostemon cablin*, *O. basilicum*=*Ocimum basilicum*, *S. officinalis*=*Salvia officinalis*, *M. alternifolia*=*Melaleuca alternifolia*, *S. cumini*=*Syzygium cumini*, *E. sideroxylon*=*Eucalyptus sideroxylon*, *E. torquata*=*Eucalyptus torquata*, *E. largiflorens*=*Eucalyptus largiflorens*, *P. harmala*=*Peganum harmala*, *O. subscorpioidea*=*Olax subscorpioidea*, *E. angustifolium*=*Epilobium angustifolium*, *Z. multiflora*=*Zataria multiflora*, *S. baicalensis*=*Scutellaria baicalensis*, *M. laevigatum*=*Mindium laevigatum*, *T. spicata*=*Thymbra spicata*, *S. chusanum*=*Stenoloma chusanum*, *C. zeylanicum*=*Cinnamomum zeylanicum*, *L. nobilis*=*Laurus nobilis*, *P. granatum*=*Punica granatum*, *S. alba*=*Sonneratia alba*, *H. sabdariffa*=*Hibiscus sabdariffa*, *S. tetrandra*=*Stephania tetrandra*, *D. turbinate*=*Dorstenia turbinate*, *F. drupacea*=*Ficus drupacea*, *F. lyrata*=*Ficus lyrata*, *D. psilurus*=*Dorstenia psilurus*, *F. bubu*=*Ficus bubu*, *E. intertexta*=*Eucalyptus intertexta*, *E. globulus*=*Eucalyptus globulus*, *S. aromaticum*=*Syzygium aromaticum*, *P. rockii*=*Paeonia rockii*, *P. lanceolata*=*Plantago lanceolata*, *P. scandens*=*Plumbago scandens*, *P. bredemeyeri*=*Piper bredemeyeri*, *P. capense*=*Piper capense*, *P. nigrum*=*Piper nigrum*, *P. regnellii*=*Piper regnellii*, *P. guineense*=*Piper guineense*, *C. martinii*=*Cymbopogon martini*, *C. citratus*=*Cymbopogon citratus*, *I. cylindrical*=*Imperata cylindrical*, *A. capillus-veneris*=*Adiantum capillus-veneris*, *N. sativa*=*Nigella sativa*, *C. greggii*=*Colubrina greggii*, *F. virginiana*=*Fragaria virginiana*, *M. citrifolia*=*Morinda citrifolia*, *M. morindoides*=*Morinda morindoides*, *P. tremuloides*=*Populus tremuloides*, *S. persica*=*Salvadora persica*, *S. saponaria*=*Sapindus saponaria*, *P. cupana*=*Paullinia cupana*, *S. wightii*=*Sargassum wightii*, *B. javanica*=*Brucea javanica*, *S. nigrum*=*Solanum nigrum*, *S. melongena*=*Solanum melongena*, *L. chinense*=*Lycium chinense*, *C. sinensis*=*Camellia sinensis*, *L. graveolens*=*Lippia graveolens*, *L. origanoides*=*Lippia origanoides*, *A. barbadensis*=*Aloe barbadensis*, *A. vera*=*Aloe vera*, *C. longa*=*Curcuma longa*, *Z. officinale*=*Zingiber officinale*, *A. citratum*=*Aframomum citratum*, *A. melegueta*=*Aframomum melegueta*, *S. birrea*=*Sclerocarya birrea*, *R. coriaria*=*Rhus coriaria*, *X. parviflora*=*Xylopia parviflora*, *M. myristica*=*Monodora myristica*, *A. squamosal*=*Annona squamosal*, *X. aethiopica*=*Xylopia aethiopica*, *A. laurina*=*Anisophyllea laurina*, *C. parapsilosis*=*Candida parapsilosis*, *C. albicans*=*Candida albicans*, *C. glabrata*=*Candida glabrata*, *C. guilliermondii*=*Candida* guilliermondii, *C. krusei*=*Candida krusei*, *C. tropicalis*=*Candida tropicalis*, *C. lusitaniae*=*Candida lusitaniae*, *C. stellatoidea*=*Candida stellatoidea*, *C. dubliniensis*=*Candida dubliniensis*, *C. rugosa*=*Coprosma rugosa*, *C. kefyr*=*Candida kefyr*, *C. inconspicua*=*Conspica inconspicua*, *C. utilis*=*Caraipa utilis*, *C. famata*=*Candida famata*, *C. holmii*=*Candida holmii*, BHA=Butylated hydroxyanisole

selective antifungal activity.[158,159] The RsAFP2–GlcCer interaction can lead to increase in the permeability, Ca^{2+} influx, and growth arrest.[160] Permeabilization due to RsAFP2 is mainly due to induction of many signaling pathways associated with the formation of reactive oxygen species (ROS), apoptosis, and caspase activation.[161] Geraniol oil derived from palmarosa oil, ninde oil, rose oil, and citronella oil can disturb the uniformity of cell membrane by interrupting sterol biosynthesis and inhibition of plasma membrane ATPase which is crucial for cell survival.[162] Taxodone is a diterpenoid compound isolated from *Metasequoia glyptostroboides* and *Taxodium distichum*, can cause loss of cell membrane integrity, and increases cell permeability, thus causing rapid loss of nucleic acid, ions, and some essential metabolites.[163]

Interference with *Candida* mitochondrial respiratory chain

Respiration takes place in mitochondria that produce ATP required by all cells. The process is accompanied with the production of large amount of ROS such as hydrogen peroxide and hydroxyl radicals as by-products. ROS can cause damage to cell proteins, lipids, and DNA.[164] HsAFP1 is a plant defensin derived from *Heuchera sanguinea* that shows apoptotic action against *C. albicans* mainly due to accumulation of ROS leading to the induction of mitochondrion-dependent apoptosis.[165] Dill seed essential oil (DSEO) can inhibit mitochondrial dehydrogenases mainly due to the disruption of the citric acid cycle and thus the inhibition of ATP synthesis.[166] Furthermore, DSEO causes intracellular accumulation of ROS in *C. albicans* and hence has an antifungal activity.[166] In addition, amentoflavone derived from *Selaginella tamariscina* has been associated with the induction of mitochondrion-dependent apoptosis in *C. albicans*.[167] Lycopene is a carotenoid pigment mainly found in tomato that can cause accumulation of intracellular Ca^{2+} and interference with mitochondrial functions, such as cytochrome C release and mitochondrial depolarization, leading to caspase activation and ROS production and hence leads to mitochondrial dysfunction and apoptosis.[168]

Inhibition of *Candida* adherence

Essential oil of *Rosmarinus officinalis* showed anti-adherent activity of *C. albicans*. The biological activity of *R. officinalis* is mainly associated with its main chemical components, including cineole, limonene, and cymene.[91] *Schinus terebinthifolius* and *Croton urucurana* have also

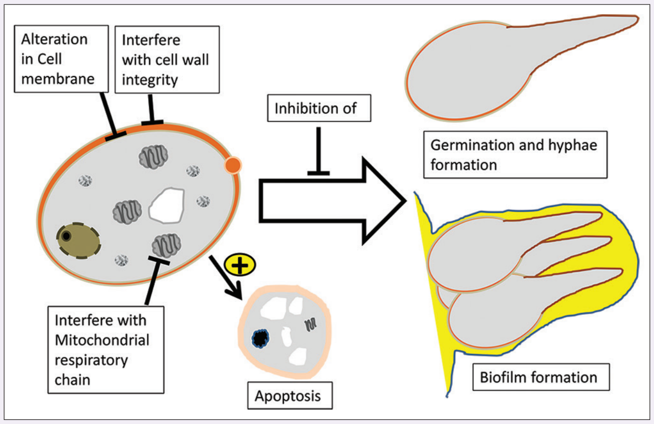

Figure 1: Representative drawing of the active sites and mechanisms of most tested plant anti-*Candida* agents

showed strong anti-adherent activity of *C. albicans* that is associated with the presence of apigenin. Apigenin can modulate gene expression and reduce the formation of glucan, leading to biofilm inhibition activity.[169]

Induction of *Candida* apoptosis

Baicalein is a flavonoid isolated from the roots of *Scutellaria baicalensis* Georgi and shows potent activity against fluconazole-resistant *C. albicans*. Baicalein mainly inhibits *C. albicans* by inducing programmed cell death (apoptosis) and reduction of drug extrusion out of the yeast cells.[170] Silibinin, a natural product extracted from *Silybum marianum* (milk thistle), can cause *Candida* apoptosis through interference with mitochondrial Ca^{2+} signaling. Ca^{2+} signaling plays an important role in physiological processes and it is associated with stress responses in fungi.[171]

Interference with *Candida* cell metabolism

Allicin isolated from *Allium sativum* (garlic) shows a strong anti-*Candida* activity mainly by inhibition of thiol-containing amino acids and proteins, therefore interfering with cell metabolism.[172] Human cells contain glutathione which can bind to allicin preventing cell damage whereas glutathione is lacking in *Candida* that makes allicin as selective and effective candidate in anti-*Candida* therapy.[173]

Interference with *Candida* cell wall integrity

Cell wall integrity is very important during growth and morphogenesis of *Candida* cells and in the face of external challenges that cause cell wall stress. Several natural products have showed interference effects with *Candida* cell wall integrity. For example, RsAFP2 defensin interacts with *Candida* cell wall GlcCers and hence damages cell wall integrity. Furthermore, it can disrupt the localization of septins and blocks the switch from yeast to hypha. The black tea polyphenols including catechins and theaflavins can cause *Candida* cell wall damage.[144] Similarly, casuarinin isolated from *Plinia cauliflora* can target *C. albicans* cell wall, leading to significant changes in the cell wall architecture including the outer glycoprotein layer and cell wall porosity.[174]

RESISTANCE OF *CANDIDA* TO PLANT NATURAL PRODUCTS

Candida strains lacking GlcCer in their membranes, either because of nonfunctional synthase enzyme or its complete absence (as in *Saccharomyces cerevisiae* or *C. glabrata*), are resistant to RsAFP2 and hence protected from cell permeabilization.[160] *C. tropicalis* shows resistance against *Uncaria tomentosa*, mainly due to the enhanced ability of *Candida* to form biofilms.[175]

TOXICITY OF NATURAL ANTI-*CANDIDA* PRODUCTS

The cytotoxic activities of anti-*Candida* natural products are rarely investigated and only few products have been tested. For example, the toxicity of geraniol oil was measured by hemolytic assay on human erythrocytes. Geraniol oil caused only 1% cell lysis at 5 µg/mL MIC compared to 10% lysis by amphotericin B or fluconazole at same tested concentrations, suggesting the safety of geraniol.[162] The cytotoxicity of *Morinda royoc* L extract was also investigated on vero cells (African green monkey kidney cells). *M. royoc* L extract showed no toxic activities according to criteria established by the American National Cancer Institute (IC_{50} ≥200 mcg/mL).[176] Furthermore, oral administration of *M. royoc* in rats showed no toxic effects, suggesting that *M. royoc* is a good anti-*Candida* product.[177]

IN VIVO INVESTIGATION OF NATURAL ANTI-*CANDIDA* AGENTS

The anti-candidal activities of suppositories made from saponins derived from *Solanum chrysotrichum* were investigated in vulvovaginal candidiasis mice model. *S. chrysotrichum* treatment showed no significant difference in clinical effectiveness compared to ketoconazole.[178] On the other hand, garlic tablets (Garcin) showed similar activity to fluconazole on *Candida* vaginitis in women admitted to a health-care center in Iran, suggesting that garlic could be an alternative to fluconazole in the treatment of *Candida* infection.[179] *U. tomentosa* extract was clinically investigated in fifty patients with denture stomatitis. *U. tomentosa* is effective as miconazole on *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*; however, *C. tropicalis* showed resistance due to its ability to biofilm formation.[175] The anti-candidal activity of *Cassia fistula* seeds was tested in mice model. The seed extract showed 6-fold decrease in *C. albicans* in blood samples and kidneys of the tested animals.[73,180]

FUTURE PROSPECTIVE AND BIOTECHNOLOGY ADVANCES IN THE PRODUCTION OF ANTI-*CANDIDA*-ACTIVE PLANTS

The need for new anti-*Candida* agents is increasing, especially with the emergence of resistant *Candida* strains. The effectiveness of natural agents against different strains of fungi, particularly *Candida*, is confirmed in several publications. It has been reported that many patencies are using natural products as anti-*Candida*. For example, *Indigo naturalis* or indigo-producing plant extract has been used in the topical treatment of candidiasis.[181] A patent made from oral herbal preparation developed by Piramal Life Sciences showed efficient activity against oral candidiasis.[182] Pharmalp developed an anti-candidal formula derived from *Epilobium parviflorum* for the use in the prevention and/or treatment of *Candida* infection.[183]

The screening for anti-*Candida* natural active products increased significantly during the past two decades. Several investigations have assessed the anti-*Candida* activities of natural products of plants from different geographical regions in the world. For example, Duarte *et al*. examined the anti-*Candida* activities of extracts of 258 Brazilian medicinal plant species.[184] However, other regions are still in the preliminary investigation stages such as the Arabian deserts. Desert plants of the arid/hyperarid climates of the Arab Gulf region are exposed to several environmental stresses, such as heat, drought, and salinity.

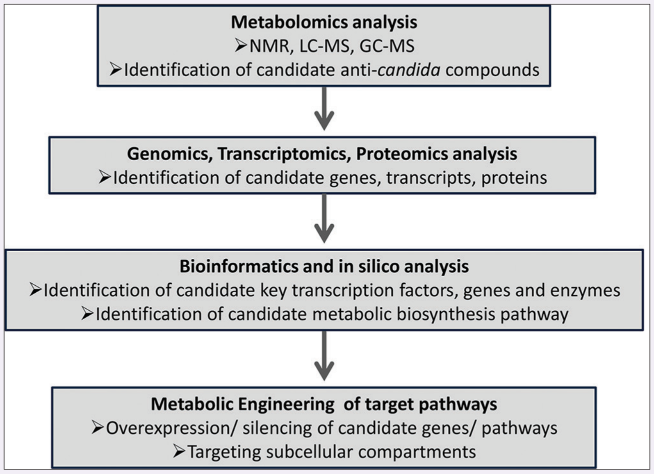

Figure 2: Simplified flow chart showing the utilization of different biotechnological approaches for identifying, developing, and enhancing the production levels of anti-*Candida* candidate compounds from a plant source

Such stresses may provide new active compounds which might have effective and unique anti-*Candida* activities.

On the other hand, modern biotechnology techniques can improve the activity of plant extracts including anti-*Candida*; for example, the development of nanostructure lipid system. Nanostructure lipid system can improve the antimicrobial activity of plant extract, reduce the required doses, and reduce side effects. Nanostructure lipid system improves the anti-*Candida* activity of aqueous ethanol extract of stems and leaves of *Astronium* sp.[185] The nanostructure lipid system can reduce the MIC of the plant extract ~ 9 times. Nanostructure lipid system can efficiently compartmentalize specific active components and modify their properties and behavior of plant extracts in a biological environment.[125] Moreover, recent advances in metabolomics and engineering of target pathways may provide an optimized commercial production of the natural compounds and enhancement of their activity. Usually, metabolomics using various bioanalytical tools such as nuclear magnetic resonance, liquid chromatography-mass spectrometry (MS), and gas chromatography-MS can be done to identify the potential anti-*Candida* compounds. Once these compounds are identified and their biosynthetic pathways are assigned, candidate genes can be identified *in silico* [Figure 2]. Consequently, target pathways can be engineered with overexpression of the desired transcription factors and genes or silencing of the undesired competitive genes and pathways to enhance their production levels [Figure 2].

CONCLUSION

As concluding remarks, several plant natural products have been tested for anti-*Candida* activities. Several of these plant products can target critical processes in *Candida* biological activities including cell wall integrity, cell membrane plasticity, cell metabolism, respiratory chain, adherence to host cell, germination and biofilm formation, or induction of apoptosis. Despite these great anti-*Candida* activities of plant products compared to controls, only few have been tested *in vivo* and none of them have ever been clinically used as anti-*Candida*. On the other hand, although some of these products including garlic, probiotics, peppermint, cinnamon, ginger, and propolis are present in the pharmaceutical market for other medical purposes, they have never been used as anti-*Candida*. The need for new anti-*Candida* is urgent since *Candida* is known as a serious resistant microbe, and hence promotion of some of the selected plant products for clinical testing will be beneficial.

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Conflicts of interest

There are no conflicts of interest.

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